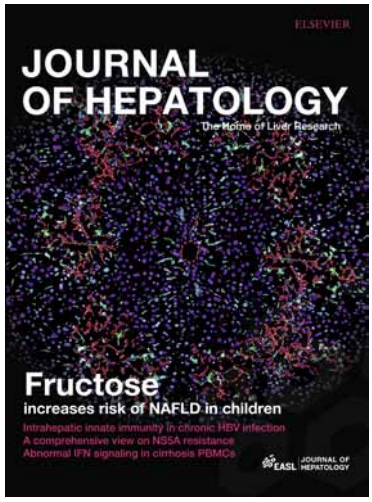

Grand Rounds

Grand Round: Autoimmune Hepatitis

Palak J. Trivedi, Stefan G Hubscher, Michael Heneghan, Dermot Gleeson, Gideon M. Hirschfield

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Grand Round: Autoimmune Hepatitis

Palak J. Trivedi,[1,2,3] Stefan G Hubscher,[1,2,3,4] Michael Heneghan,[5] Dermot Gleeson[6] and Gideon M. Hirschfield.[1,2, 3,6,7]

1. Centre for Liver and Gastroenterology Research, National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, UK
2. Liver Unit, University Hospitals Birmingham, Birmingham, UK
3. Institute of Immunology and Immunotherapy, University of Birmingham, UK
4. Dept. of Cellular Pathology, University Hospitals Birmingham, UK
5. Institute of Liver Studies, King's College Hospital, London, UK
6. Liver Unit, Sheffield Teaching Hospitals Foundation Trust, UK
7. Toronto Centre for Liver Disease, University of Toronto and University Health Network, Toronto, Canada

Correspondence:

Gideon M. Hirschfield, Lily and Terry Horner Chair in Autoimmune Liver Disease Research, Toronto Centre for Liver Disease, Department of Medicine, University of Toronto, Toronto, Canada.

Email: gideon.hirschfield@uhn.ca

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ABSTRACT

Autoimmune hepatitis (AIH) is a corticosteroid responsive, autoimmune liver disease arising consequent to immunogenetic and environmental risk factors. The clinical course reflects relapsing and remitting, hepatocyte targeted, immunologic damage, countered by reparative responses to cell injury. Appropriate and timely immunosuppressive therapy drives disease into remission, albeit accompanied by inevitable side effects. Many challenges faced in the clinic reflect practice that must capture a heterogeneous disease presentation, course, and treatment response, as well as treatment tolerability. In this grand round we appraise the evidence supporting currently applied treatment approaches, address the impact of autoimmune liver disease 'crossover or overlap' presentations, explore important clinical correlates to immune-serological classifiers, and discuss the factors influencing choice of alternative therapy in difficult-to-treat situations.

Vignette

A 19-year old woman (body mass index [BMI] 45.6 kg/m^2) presented with a 6-week history of malaise, nausea and progressive jaundice, without features of liver decompensation. Serum tests showed an alanine transaminase (ALT) of 592 IU/L (upper limit of normal [ULN] 40 IU/L), bilirubin of 426 μmol/L (ULN 21 μmol/L), serum IgG 20.89 g/L (ULN 16.10 g/L), and seropositivity for anti-nuclear antibodies (ANA; titre 1:100; homogeneous) and anti-smooth muscle antibodies (ASMA). An extended viral screen was negative (hepatitis A, B, C and E; Epstein Barr Virus; Human Immunodeficiency Virus and Cytomegalovirus). Liver biopsy showed features of acute lobular hepatitis compatible with acute autoimmune hepatitis (AIH). There was moderately severe inflammatory activity including foci of bridging necrosis. No steatosis was evident. On starting oral Prednisolone (20mg daily; 0.25mg/kg/d), biochemical and immunological remission resulted within 1 month (**Figure 1A**). Azathioprine was introduced (when bilirubin <100 μmol/L) alongside gradual tapering in Prednisolone.

The patient sustained biochemical and immunological remission for a period of 16 months on Azathioprine monotherapy, however she failed to attend clinic visits during the following year. The patient later represented with generalised fatigue, malaise, a markedly elevated serum ALT (628 IU/L, bilirubin 20 μmol/L), and reported poor adherence to treatment over the past 10 months. Whilst remission could be induced with oral Prednisolone once again (20mg daily), maintenance proved difficult despite reintroduction of Azathioprine (2mg/kg/d). Ongoing biochemical and immunological activity was evident whenever Prednisolone dosage was tapered below 15mg/day, and Azathioprine metabolite monitoring revealed sub-therapeutic 6-

thioguanine nucleotide values (178 pmol/8 $x10^8$ cells; normal range 235-450 pmol/8 $x10^8$ cells). The patient was trialled on allopurinol (100mg daily) to counteract methylmercaptopurine shunting [1], but unfortunately developed significant side effects (nausea/abdominal pain – allopurinol stopped) and inflammatory indices remained abnormal (ALT 866 IU/L, bilirubin 20 μmol/L, IgG 37.64 g/L). Given the young presenting age and difficult to treat disease, a magnetic resonance cholangiogram (MRCP) was performed; however no features of primary sclerosing cholangitis were evident.

Drug intolerance together with inability to attain therapeutic thiopurine metabolite values led to trial of alternative immunosuppression; first Mycophenolate mofetil (MMF; with appropriate counselling regarding contraception) and later Tacrolimus [2]. Ultimately however, the patient continued to manifest features of active hepatitis despite therapy, necessitating repeated courses of high-dosage Prednisolone (>30mg daily) to the point of developing Cushing's syndrome with very difficult glycaemic control. An attempt to switch Prednisolone to Budesonide was also made [3,4]; however ongoing inflammatory activity persisted. A repeat liver biopsy obtained 5 years after the initial presentation showed features of chronic hepatitis with moderate interface hepatitis and bridging fibrosis. There was also ongoing lobular inflammation, moderate in severity with foci of centrilobular necrosis. To this effect the patient received intravenous rituximab. This led to successful biochemical remission until the time of writing (approximately 12 months) and marked improvement in serum immunology (ALT 15 IU/L and IgG 17.93 g/L, respectively) (**Figure 1B**).

DISCUSSION

The patient description raises pertinent clinical questions relevant to the optimal management of AIH:

How to guide decision making in use of therapy?

AIH is a persistent and relapsing immune-mediated liver injury characterised by (often chronic) hepatitis of varying severity, which carries significant risk of developing end-stage liver disease unless treated by timely and effective therapy. Our understanding of aetiological drivers is incomplete, but mixed environmental, genetic and epigenetic drivers of inflammation are all presumed relevant. For example strong *HLA* associations exist for disease risk, and non-*HLA* genetic variants (some rare but functional e.g. in the genes *AIRE*, *GATA-2*, *CTLA-4*, others common e.g. in the gene locus for *SH2B3* but without clear-cut coding impact) have been identified. The paradigm of drug induced AIH, such as with Nitrofurantoin, as well as the identification of *HLA* as a strong risk factor in many drug induced liver injuries, supports how environmental triggers can precipitate immune injury. Furthermore, the insight that indeed other autoimmune diseases are not as frequent in family members as initially expected indicates the importance of environmental triggers. Ongoing research is focused on harnessing a better understanding of the ongoing subtle, but deleterious changes in immunoregulation that represent disease drivers, as well as therapeutic targets [5].

Determining activity, severity and chronicity of disease

Approaches to treatment derive from historic placebo-controlled trials, in which those with untreated moderate-severe AIH (AST >5xULN, globulins >2xULN, liver biopsy

showing confluent necrosis) had a very poor prognosis, with 5 and 10-year survival of 50% and 10% respectively. Treated 10-year transplant-free survival rates, by contrast, approximate 90% [6–10], accepting however that intent is usually with regard to much longer term outcome.

Current guidelines recommend liver biopsy at the time of first presentation [6,7]; which is a critical tool for identifying features that are supportive of diagnosis, determining disease severity (inflammatory activity and fibrosis stage), and discriminating acute vs. chronic presentations (**Figure 1C and 1D)**. Classical histological findings of chronic AIH include lymphoplasmacytic infiltration, predominantly located in portal tracts and associated with varying degrees of interface hepatitis. Other typical features of AIH, although not universally present, are rosette formation, emperipolesis and plasma cell enrichment. Interface hepatitis is associated with the development of periportal fibrosis, which may progress to bridging fibrosis and ultimately lead to cirrhosis. By contrast, lobular inflammation predominates in patients with an acute presentation, in addition to typical hepatocyte ballooning, lobular disarray and spotty hepatocyte apoptosis/necrosis. More severe cases may be associated with extensive hepatocyte necrosis, ranging from confluent necrosis through bridging necrosis to panacinar or multiacinar necrosis (**Figure 1D**). The latter is typically seen in cases presenting with signs of acute liver failure. Similar changes can also be seen in cases of acute viral or drug-induced hepatitis. Features favouring AIH as a likely cause of acute hepatitis include prominent portal inflammation with interface hepatitis (resembling changes seen in chronic AIH), a plasma-cell rich inflammatory infiltrate, lymphoid aggregates and centrilobular accentuation of inflammation (central perivenulitis). Emperipolesis and hepatocyte rosettes are less

helpful in diagnosing AIH with an acute presentation as these changes are also frequently present in other causes of acute lobular hepatitis [11].

The mononuclear infiltrate of AIH tends to be predominated by $CD4^+$ T-cells that localise to the periportal areas with hepatocyte damage thought to include apoptosis induction and direct effects of the cytokines interferon-γ, tumour necrosis factor α and interleukin (IL)-17. Disease-specific increases of IL-17 in both the peripheral blood and liver are reported, and it is proposed that differentiation into T_h17 as oppose to regulatory T-cell (T_{reg}) phenotypes underlie the pro-inflammatory nature of immune-mediated liver injury. $CD8^+$ T-cells, by contrast to their $CD4^+$ counterparts, more often localise to the areas of interface activity, and are overall less prevalent than in other causes of hepatitis. Nevertheless $CD8^+$ T-cells are highly activated in AIH, demonstrating an upregulation of several cytotoxic molecules including granzyme B and perforin, and resistance to the anti-proliferative effects of T_{reg} *in vitro*. Plasma cells, which develop from activated B-cells, are also numerous in AIH livers. The observed correlation between intra-portal B-cell numbers and serum IgG values, together with case series supporting efficacy of the B-cell depleting agent rituximab in AIH lend further support to their role in disease pathogenesis. This aligns with an increased understanding of the role B-cells play in regulating T-cell function (B-cell depletion favouring T_{reg} function) [5].

High-risk disease

At least one-third of adults have cirrhosis at diagnosis [8,9], conferring a heightened mortality risk and/or need for transplantation (hazard ratio 21.25) [9]. Offering treatment to avoid transplantation is deemed mandatory in all patients with advanced

fibrosis, and for those with established, compensated liver cirrhosis and persistent inflammatory activity [6,7]. By contrast, when patients present with overt hepatic decompensation, then the risk versus benefit is less apparent. If experience and expertise are not available locally, then immunosuppression should be administered only following discussion with a transplant unit and when inflammatory activity is overt histologically.

The merits of immunosuppression for patients with inactive ("burned out") cirrhosis are contentious, given that inflammatory activity (hepatitis) is prerequisite for diagnosis. In any event, the impact on overall outcome is generally thought to be very low for this subgroup, leaving just the risk of drug-related side effects [7]. It is therefore reasonable for the patient presenting with 'burned out' AIH to receive no direct immunosuppression, but they must still be monitored and surveyed.

Acute-severe (AS)-AIH presentations, and in particular those with fulminant hepatic failure are additional groups who may not necessarily benefit from immunosuppression. AS-AIH is defined by an acute onset of symptoms to presentation of <26 weeks, associated with significant hepatic dysfunction (INR $\geqslant$1.5) that develops at any time during the index presentation, despite the absence of chronic disease features on liver histology [12]. Important in managing such patients is the careful attention to prevention and treatment of inter-current sepsis and management in the context of expectant transplantation. The short-term mortality approaches ~20%, with 60% of patients needing a liver transplant [12]. Thus it is advised that immunosuppression only be trialled in close liaison with a transplant

unit, whilst seeking early evidence of therapy response (e.g. falling bilirubin) or lack thereof.

Mild disease

The benefits of treatment in those classified as 'asymptomatic' are also debated. The 10-year survival in this group is 80% based on historical data, therefore mirroring that of the overall AIH population. However an Italian group reported patients with asymptomatic disease (n=90) compared to symptomatic presentations (n=215) as exhibiting lower mean serum ALT values (7 vs. 23xULN), lower serum bilirubin (1.4 vs. 8.6mg/dL) and milder histological disease activity (histological activity index [HAI]: 7 vs. 9). Nevertheless, development of cirrhosis (18.5% vs. 12.2%), and event-free survival – defined as any episode of decompensation, hepatocellular carcinoma, listing for liver transplantation or death – developed at a similar rate in asymptomatic vs. symptomatic patients (22 vs. 24%) [13]. Furthermore, 25% of asymptomatic patients may go on to develop symptoms during follow-up with fluctuating histological inflammatory activity; and whilst improvement in biochemical indices may occur spontaneously, resolution of inflammation is less frequent in untreated patients (12% vs. 63%) [14]. These data indicate that an absence of symptoms must not be a factor determining whether or not to treat patients. In fact, data to support empirical treatment in this group stems from data in patients of older age, 25% of whom are asymptomatic yet more likely to be cirrhotic at presentation (odds ratio [OR]: 1.58) [15]. Elderly patients respond well to treatment, and relapse less commonly on treatment withdrawal compared to patients of younger age onset (OR: 0.38) [15,16]. Equally, non-severe presentations with mild interface hepatitis and modest biochemical changes (normal serum bilirubin, serum transaminase values

<5xULN) may not necessarily follow a sedentary course, and mild AIH can be interspersed with phases of severe activity that can be aggressive.

What constitutes effective therapy?

Treatment goals need to be personalised; resolution of liver biochemistry can be achieved in ~75% of patients, of which ~80% also attain normal serum immunoglobulin values [9]. Between 39% to 65% of patients normalise serum ALT within six months of starting treatment (93% at 1 year) [3,8,16]. Failure to attain normal transaminases by 6-12 months confers an increased risk of liver transplantation / liver-related death (HR 4.8); whereas complete biochemical and immunological remission (serum transaminases, bilirubin and IgG values all ≤ULN) associates with reduced histological disease activity, regression of liver stiffness as assessed by transient elastography, and can predict histological fibrosis regression after a median of 5.5 years (range 1-9.7 yrs.; relative risk [RR]: 3.66) [17]. However histological improvement lags behind normalisation of laboratory values by at least 6-12 months [10,18]; and failure to attain remission histologically despite doing so biochemically is associated with >2-fold increased risk of progression to transplantation and all-cause mortality [10].

Inducing remission

With good reason (efficacy) corticosteroids, either Prednisolone or Budesonide, are the mainstay for inducing remission in most patients. Corticosteroids alone or in combination with Azathioprine are considered equally effective, although an individualised approach is needed to ensure the best long-term outcomes for patients. Combination therapy can be instituted either at diagnosis, or quite reasonably with a

slight delay of 2-4 weeks in starting Azathioprine, which is without detriment to long-term disease control.

Many treatment algorithms have been proposed [6,7], but there is wide variation in practice, a reflection of disease heterogeneity but equally a lack of real-world consensus on the value of immunosuppression intensity to the individual patient (**Table 1**) [19]. A brief report from Hamburg suggested that high prednisolone dosages result in more rapid normalisation of serum transaminases [20], although whether they are universally necessary in view of side effects (and equally whether they confer better long term outcomes) is unclear; particularly given the heterogeneity in disease presentation and challenges in identifying at baseline patients most in need of 'high-intensity' immunosuppression. As the patient in our vignette shows, a severe presentation is not correlated with an absolute need for high dose Prednisolone to induce good disease control. Moreover there is widespread concern about weight gain and cosmetic impact, in addition to the burden of depressive symptoms, related treatment non-adherence, and reduced health-related quality of life associated with corticosteroids [21,22]. Important factors related to dose and corticosteroid choice must include the presence of obesity, metabolic bone disease, diabetes, hypertension or concern over cosmetic side effects of Prednisolone, as well as clinician concern for adherence. Budesonide has higher affinity for the glucocorticoid receptor than Prednisolone but undergoes over 90% hepatic first pass metabolism, the resulting catabolites being devoid of glucocorticoid activity thus limiting corticosteroid related side effects. Despite improved tolerability with Budesonide, advanced liver disease or porto-systemic shunts pose a risk for corticosteroid-induced side effects as a result of altered hepatic clearance and increased systemic availability. For this reason the

labelled indication excludes individuals with cirrhosis. In the context of severe presentations of AIH, or as switch-over therapy for side effects, more efficacy data is needed [4].

Azathioprine monotherapy is largely inappropriate for inducing remission, given its slow onset of action and poorer patient outcomes when monotherapy is compared to Prednisolone alone or Prednisolone/Azathioprine in combination [23]. However there are very occasional patients with mild disease activity, no liver fibrosis, and good clinical or personal reasons to avoid corticosteroids, in whom monotherapy with azathioprine from the outset, with equivalent treatment goals, can be rarely considered.

Maintaining remission

In most, corticosteroids are combined (once an initial response is confirmed) with long-acting immunomodulators during the induction phase [19]. Whilst drug-induced hepatotoxicity is uncommon, phased introduction of Azathioprine is pragmatically helpful in managing and traversing the side effects of treatment. It is also notable that outcome data in a non-transplant specialist programme identified non-treatment with Azathioprine as a risk factor for progression to liver transplantation and liver-related death (HR 3.96), as well as all-cause mortality (HR 2.71) [8].

Once achieved, biochemical remission can be maintained in the majority of patients with Prednisolone (gradually tapered to ~7.5-12.5mg/day), alongside Azathioprine 1-2mg/kg/day. Higher dosages of Azathioprine (2mg/kg/day) may be needed when bridging to monotherapy, but this can be tailored to individual response. At higher

doses the risks of Azathioprine induced malignancy, especially in those over the age of 60, is an important consideration as highlighted by recent IBD literature. Thiopurine metabolite monitoring may have a role, but at present is usually limited to those in need of intensified treatment or where drug adherence is a concern [24].

Whilst disease control can be achieved and sustained with a very small dose of corticosteroids, Prednisolone monotherapy has a limited role in maintaining remission. This approach is largely reserved for patients intolerant or refractory to immunomodulators, and for patients whom the avoidance of side effects from therapy such as Azathioprine may be of greater concern. In such situations it can occasionally be reasonable to use monotherapy with corticosteroids from the very outset with no planned addition of Azathioprine or equivalent. In the authors' experience, this is often in the quite elderly patient, for whom excellent response to treatment can be sustained with very modest Prednisolone dosages (e.g. 2.5mg or 5mg per day). The efficacy and long-term safety of Budesonide maintenance monotherapy is also currently unknown, albeit anecdotally, can be considered in selected patients.

Duration of therapy

Although there is no consensus on optimal duration, current guidelines recommend treatment be continued for long enough to make histological resolution 'likely' [6]. Twelve months is probably inadequate given the relatively low histological remission rate; but for non-cirrhotic patients with type-I AIH, who are SLA negative, a finite duration with corticosteroids for 18-24 months and Azathioprine for 3-5 years, prior to a single trial off therapy provided transaminases and IgG have remained normal during this time, is reasonable to discuss with patients.

Tapering of corticosteroids without repeat liver biopsy, provided full biochemical and immunological remission has been attained, is based on data showing correlation with a lower hepatic activity index (HAI<4) in 18/22 patients prospectively followed up over a median of 5.6 years [18]. However, ~45% of patients who maintain a serum ALT and globulin value within the normal range will have persisting histological activity (HAI ≥4) [10]. This is associated with heightened need for liver transplantation and increased all-cause mortality (HR 3.1). However, it is not known whether treatment intensification is beneficial.

Between 41-55% of patients eventually develop an episode of relapse (an increase in serum ALT ≥3xULN ± an increase in serum IgG >20g/L) after attaining remission, despite ongoing therapy [8,9]. The odds appears to be lower in patients of older presenting age (≥18 years; odds ratio [OR]: 0.29), and heightened in those who are HLADRB1*04:01 positive (0R: 2.3). Disease relapse and loss of remission (increase in serum ALT >ULN) are a particular issue after tapering or cessation of treatment. The Dutch AIH working Group have reported a relapse rate of 59%, 81% and 88% at 1, 3 and 5 years, respectively, even when treatment was tapered and/or discontinued after clinical and biochemical remission had been sustained for ≥2 years [25]. The incidence of relapse appeared greater when tapering of medication was trialled in younger patients (age <45 years) and those still requiring combination therapy (overall rate of relapse or loss of response: 59% vs. 19% in Prednisolone/Azathioprine combination and Azathioprine monotherapy arms, respectively). Azathioprine monotherapy is as effective at maintaining remission as dual therapy with Prednisolone/Azathioprine, and also associated with fewer side effects [26]. It is

therefore common practice to attempt use of Azathioprine monotherapy in patients who have attained sustained remission (approximately 18 – 24 months) without prior history of relapse.

Relapse is more likely to occur on treatment withdrawal in the event persistent histological inflammatory activity is present (HAI >3). Thus it has been advised that biopsy be performed routinely for all patients prior to trialling cessation of therapy [7]. However, data from a small European cohort showed that approximately 50% of patients still require re-treatment despite having an absence of inflammatory activity (HAI≤3). Further insights into the predictive components of liver histology stem from a study in the United States (n=88), which indicated persistence of plasma cells in the portal tracts as the sole critical factor in determining risk of relapse, whilst median HAI was no different between relapsers vs. non-relapsers [27].

Whilst it is a valid perspective to biopsy prior to treatment withdrawal, a paradigm that is more selective in the use of liver biopsy is equally reasonable, with the important practice point for ALL patients who stop therapy to be monitored closely for relapse. The nature of clinical practice is also relevant: clinicians managing large cohorts of patients with AIH may be better placed to identify heterogeneity in disease course such that liver biopsy, for example prior to treatment withdrawal, is less frequently of clinical utility. Whereas those with broader clinical programmes in whom AIH is much less frequent, may find the information added by an additional measure of disease activity, in particular histology, helpful.

Populations with added clinical challenges

Development of PSC and relevance to clinical practice

Whilst a single diagnostic test does not exist for AIH [1], a series of weighted criteria devised by the International AIH Group (IAIHG) can facilitate some uniformity in diagnosis. At the time of development, the principled intent was to ensure comparability of patient populations in clinical research. Therefore the IAIHG scoring system should not be applied as a discriminative diagnostic index implying that manifestations of AIH are somehow unique, and can be siloed within disease-specific borders. Manifestations that are also common to PSC and primary biliary cholangitis (PBC), include interface hepatitis, presence of autoantibodies and elevated serum immunoglobulin concentrations [28]. Overlap 'features' be they biochemical, serological, histological or radiological, are hence frequently shared across all three autoimmune liver diseases, with some less categorical and objective than others.

Accepting these caveats, the IAIHG propose that "although patients may have overlapping features across the spectrum of autoimmune liver injury, individual cases should be categorised according to the predominant disease entity; and that the IAIHG scoring system should not be used to diagnose distinct subgroups of patients [29]." An appraisal of disease phenotype must be performed longitudinally rather than at a single point in time, which is particularly relevant for those of younger presenting age. Of note, ~50% of paediatric patients with typical biochemical and immunological features of AIH can manifest a cholangiographic phenotype indicative of sclerosing cholangitis [30]. This group enter biochemical remission less often than those with a 'pure' AIH phenotype (83% vs. 100%), and experience relapses characterised by elevations in serum gamma glutamyl transpeptidase (γGT) [30]. Cholangiographic

abnormalities also evolve in 10-24% of adult AIH patients [31,32], and as expected, more predominant in patients of younger presenting age (24 vs. 39 yrs. in one study). The prevalence of features of AIH within the International PSC Study Group ([IPSCSG; n=7,121), was approximately 7% (n=470) of PSC patients [33]. However, with no codified diagnostic approach, the proportion of overlap cases relative to PSC varied widely between contributing centres, being heavily influenced by location (Australia, 2%; North America, 3%; Western Europe, 6%; Northern Europe, 7%; Southern Europe, 8%; Central Europe, 10%).

Patterns of liver biochemistry in PSC are influenced by age at presentation, and a 'hepatitic' laboratory profile does not automatically equal AIH overlap. In our programme we have shown a negative correlation between presenting age vs. serum ALP (Spearman's rho 0.247; p=0.009) and vs. the serum AST:ALP ratio in PSC specifically (Spearman's rho: -0.253; p = 0.007) [34]. Moreover, >50% of PSC patients presenting between 18 to 25 years of age displayed a serum AST value >2xULN; vs. ≤30% in groups aged >25-43 years, 43-55 years and >55 years (n=112 overall; p=0.03).

The development of PSC must be considered in AIH patients who are poorly responsive to immunosuppressive therapy [35,36], however as the radiological hallmark of PSC (beading and stricturing of the biliary tree on cholangiography) is a late manifestation, the exact interval between onset of AIH and PSC is difficult to determine. Key to practice is the fact that no significant differences in transplant-free survival were seen in the IPSCSG cohort which compared adult patients having classical PSC vs. those with PSC/AIH (incidence rate [IR] of liver

transplant/mortality: 5.62 vs. 4.70 per 100 pt.-yrs, p=n.s. [33]). This observation was mirrored in a multi-centre paediatric study of 781 children with PSC (5-year event-free survival: 88% vs. 90% [37]).

As AIH evolves to PSC clinically, typical histological features of AIH such as portal inflammation and interface hepatitis tend to subside, likely reflecting successful therapeutic suppression of inflammation, and features of chronic biliary disease become more prominent. The changes seen include bile duct loss, ductular reaction often associated with a 'biliary pattern' of interface activity and fibrosis, and features of chronic cholestasis including the accumulation of copper and copper-associated protein in periportal hepatocytes. Classical 'onion-skin' foci of periductal fibrosis mainly involve medium sized ducts and are thus seen infrequently in needle biopsy specimens. Liver biopsy is still helpful in this setting, both in identifying the presence of ongoing inflammation, and in detecting features of chronic biliary disease, which may prompt additional investigations and provoke alternative management strategies (**Figure 1E**).

A longitudinal approach to care must be adopted when managing autoimmune liver disease, focusing on clarity and accuracy in disease definition and rationale for treatment. This is particularly relevant when immunosuppression is offered to patients with PSC and overlapping AIH features; an intervention not supported by evidence of benefit. Conventional remission criteria for AIH cannot be applied to patients with PSC, who may develop progressive liver disease irrespective of whether they normalise AST, ALT and/or immunological parameters [38].

Phenotypic differences between adult-onset AIH type-I and type-II

Attempts to sub-classify AIH based on serological phenotypes are frequently described, and the nature of autoantibodies can fluctuate before and after immunosuppressive therapy [39]. Approximately 65% of all patients will test positive for ANA and/or ASMA, which although non-disease specific are considered representative of Type-I AIH [40]. By contrast, anti-LKM-1 and anti liver cytosol (LC)-1 antibodies typify type-II disease. Across some settings, the latter accounts for ~25% of AIH in children, and importantly, liver cirrhosis may already be established in 60% of at time of diagnosis. Early reports from the 1980s also suggested that this group of children more often present with fulminant hepatic failure than contemporaries with type-I AIH.

Seropositivity against soluble liver antigen / liver pancreas antigen (anti-SLA/LP) is found in 22% of AIH patients [9], mostly in type-I disease. Indeed, ~90% of anti-SLA/LP cases will also test positive for ANA and or ASMA, whereas coexistence with anti-LKM is rare. Anti-SLA/LP positivity may characterise a high-risk group for disease progression (HR for liver transplantation / death: 4.25 [9]), although this observation needs validation [39].

Type-I AIH contributes ~90% of adult cases, with an average 'quoted' diagnosis age between 36-56 years, supporting the concept of two patterns of age related presentation [8,25]. By contrast, frequently fewer (2-10%) adult cases are contributed to by type-II AIH, although treatment paradigms do not tend to differentiate between serological phenotypes [9,41]. Nevertheless, therapeutic failures defined as the

presence of clinical/biochemical deterioration despite medication, appear to be less common in ANA-positive vs. negative patients (7% vs. 24%, p=0.016 [39]).

The UK multi-centre audit confirmed Type 2 disease as associated more commonly with liver cirrhosis at diagnosis (47% vs. 25%; p=0.04) [41]. This is in contrast to an Italian group, who found no differences on comparing age- and sex-matched cohorts with regard to the frequency of cirrhotic presentations (12% vs. 19%, p=0.456), proportion attaining complete treatment response (50% vs. 60%, p=0.464), null responders (12.5% vs. 15%, p=0.788) and the number who relapse (81% vs. 78%, p=0.961) [42,43]. The nature of IgG elevation may also differ in adults, and be misleading as to severity of disease and it's monitoring. Indeed, in our programme serum IgG values rarely become elevated in adult-onset LKM-1 positive AIH, even at the peak of hepatitis activity (**Table 2**).

Pregnancy

Pregnancy and AIH is another important area for discussion, and post-partum disease flares can be significant irrespective of AIH subtype, occurring in 25-30% of pregnancies. Disease flares are linked to poor disease control in the year prior to pregnancy, an absence of therapy whilst pregnant, and a significantly increased risk of hepatic decompensation and increased need for neonatal admission to special care baby units [44]. It is therefore critical that immunosuppression be continued during pregnancy and into the post-partum period, during which more active disease can be anticipated, and intensified monitoring and intervention offered as appropriate.

How is second-line therapy applied in clinical practice?

Defining treatment failure

Poor adherence is the first consideration during incidents of therapeutic failure, although deviation from the expected clinical course also warrants re-evaluation of diagnosis, exclusion of sclerosing cholangitis, and potentially drug malabsorption from poorly-controlled coeliac disease [21,28]. Assuming adherence and a correct diagnosis, patients who do not show clinical or laboratory improvement within 6 months of starting 1st line therapy (10-15%) are deemed unresponsive, whereas those who deteriorate by any clinical or laboratory parameter despite compliance (~9%) are considered treatment failures. Of concern, failure to normalise serum ALT within 6-12 months of presentation is associated with an >5-fold increased risk of liver-related death or transplantation [8,16] and such situations justify the reinstitution of Prednisolone (variable dose depending on clinical setting) alone or in conjunction with Azathioprine (2mg/kg/day). High dose corticosteroids, if chosen, are maintained for at least 1 month. Thereafter, the corticosteroid dose may be reduced according to clinical response.

Continued deterioration despite the above measures may be an indication for alternative therapies, but obtaining histological evidence to confirm ongoing inflammatory disease is advised to ensure accurate diagnosis. This can help stratify treatment decisions, wherein the threshold to trial salvage therapies or triage to liver transplant assessment may be guided by the acuteness and severity of injury in the correct clinical context. Mostly, however, alternative therapies are needed because of drug intolerability (side-effects or complications) rather than corticosteroid-dependency or non-response to primary therapy. Whilst the goals of treatment remain

unchanged, irrespective of the therapeutic paradigm selected, there are no randomised controlled trials to back any of the potential second-line treatments used in clinical practice.

Optimising thiopurine delivery

6-mercaptopurine (6-MP) has recently been proposed as an alternative therapeutic option for Azathioprine intolerance, although evidence for its efficacy in non-responders is lacking. In a study of 20 patients with Azathioprine intolerance, 75% exhibited biochemical response to 6-MP; 8 having complete remission and 7 a partial improvement in liver biochemistry. The remaining 5 patients ceased 6-MP therapy in view of ongoing intolerance to thiopurines [45].

Elevated concentrations of the metabolite 6-methylmercaptopurine (MMPN) have been associated with the development of hepatotoxicity and therapeutic drug failure, particularly when coexistent with lower levels of 6-TGN. Co-administration of allopurinol alongside 'low-dose' thiopurines has been shown to redirect metabolism in one small study, with patients having prior dose-limiting intolerance (n=3), non-response (n=3) or loss of response to standard thiopurine treatment [1]. All 8 patients normalised serum ALT within 1 month, in line with reduction in red blood cell 6-MMP concentrations. Although limited by size, these findings are encouraging and require long-term validation in a larger, more homogeneous cohort of AIH patients.

Mycophenolate Mofetil

Mycophenolate Mofetil (MMF) is perhaps the most well-studied therapeutic alternative to Azathioprine; and although unlicensed, is accepted as second-line

treatment by most [46,47]. Collectively, data surrounding MMF indicates use as a possible alternative for maintaining remission, largely reserved for instances when patients are intolerant of Azathioprine as opposed to non-responders. However, approximately 10-37% of patients discontinue MMF in view of adverse events-particularly sepsis [47,48]. Of further, practical concern is its reported teratogenicity, which precludes use in women planning pregnancy (and raises concerns for men as well, which are unresolved).

In the largest multi-centre cohort to date (n=121; dosage 0.5 to 2.0 g/day), the rate of complete response (normal liver biochemistry and serum IgG values) was 57% for patients with Azathioprine intolerance vs. 34% in those with prior non-response [2]. Of note, the rate of liver transplantation / liver-related mortality exceeded 10% at 5 years for MMF-treated patients, considerably greater than that evident in predominantly Azathioprine-treated cohorts [8,9]. Mycophenolate has also been detailed as first-line therapy by a group from Greece (n=109; dosage 500mg/day), and led to biochemical and immunological remission (together with Prednisolone) in 72% of treated patients within the first 18 months [48]. However, the comparator group of patients, who received more conventional treatment with Azathioprine and Prednisolone, displayed a much lower rate of complete response (46%) than shown by other reports. Our practice when using MMF is to largely aim for a dose of 1g bid, but higher (up to 3g daily) and lower (e.g. 500mg bid) doses can be appropriate in selected patients, based for example on body mass and/or disease activity.

Tacrolimus

Calcineurin inhibitors have been shown to be beneficial in inducing and maintaining biochemical remission in small numbers of patients, mostly children. Support of therapeutic efficacy in adults is lent by a multi-centre in which 58/80 patients who were either non-responsive or intolerant to Azathioprine achieved complete biochemical response [2]. Notably, the rate of complete biochemical and immunological remission in prior Azathioprine non-responders was significantly greater with Tacrolimus (1-8mg/day) vs. MMF second line therapy (0.5-2g/day); 57% vs. 34%, p=0.029), respectively, although significant side effects led to drug withdrawal in 10% of patients, with high mortality rates observed in both groups (10% vs. 13% over 5 years). Target drug trough values were not specified, although a mean level of 6 ng/mL has been cited elsewhere [7]. In our practice the target trough level is related to the relative indication- in those for whom Tacrolimus is used to adjunct to existing dual therapy the authors usually advise trough levels of 3-5ng/mL; in those for whom Tacrolimus represents the mainstay of immunosuppression, trough levels of 5-7ng/mL are more often advocated.

Biologics

The patient presented in our vignette was able to attain remission although this could not be sustained via conventional means following a period of non-adherence. Despite best efforts with thiopurine therapy she required consistently high dosages of corticosteroids and failed second-line treatment with MMF. Few salvage therapies have been identified for AIH that is recalcitrant to conventional treatment. One retrospective series has reported success in using infliximab [49], albeit with concern over side-effects. Anti-TNFα has also been associated with hepatotoxicity in a

number of case series, albeit not necessarily reflective of a classical immune-mediated process. Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen on the surface of normal and malignant B-cells. To date, there have been several small case series describing the rituximab experience in AIH, and collectively the data is promising, and supportive of the need for prospective trials. B-cell activating factor (BAFF), which belongs to the tumour necrosis factor superfamily, is also well known for its role in the survival and maturation of B-cells, and elevated in the serum of patients with AIH where values correlates with serum transaminase activity. An anti-BAFF receptor antibody therapy will be tested in a multicentre trial in AIH (NCT03217422).

Conclusion

When managing patients with AIH, a long-term longitudinal approach to care must be applied. This must focus on confidence and clarity in diagnosis, individualised assessment of risk, and clinician-patient partnership in establishing the rationale for (often lifelong) treatment in the context of clear clinical benefits in the short- and long-term, but equally adverse treatment related risks. Complete remission is an attainable and appropriate target for most patients with an associated improved transplant-free survival. However inadequate disease control, for many reasons (disease severity, treatment side-effects, adherence) alongside poor recognition of the quality-of-life impairment, remains high. Equally, care continues to address chronic suppression of persistent immune activity in contrast to offering patients ‘cure’. Didactic indications for immunosuppression remain inadequately defined for subgroups such as those manifesting asymptomatic and mild disease, ‘burned-out’ cirrhosis, or those with overlap biliary presentations. Those presenting at a young age

have added practical challenges, including often adherence to therapy, severity of disease associated with LKM/anti-LC-positive disease, fertility/pregnancy concerns, and a much greater reality of clinically meaningful biliary overlap evolution over time. There remains a need for long-term large and representative clinical cohort studies as these will add value in AIH, providing contemporaneous recognition of clinical and individual burden of disease. Such studies have the potential to help justify the evolution of our currently limited treatment paradigms, to approaches that better reflect the state-of-the-art management of more common autoimmune diseases, such as rheumatoid arthritis or ulcerative colitis.

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Table 1: Holistic care of the patient with autoimmune hepatitis

Domain	Comments
Timely and individualised therapy	- Precise regimens vary between guidelines, and in practice must be tailored to underlying inflammatory activity, disease severity and patient tolerability: - Elderly patients: may respond to lower low dosages of corticosteroids (10-20mg Prednisolone, or equivalent) to enter remission. - Pregnancy: spontaneous disease remission common, but disease relapse often manifests in the post-partum period particularly for those not on therapy during pregnancy (50% vs. 26% for women on immunosuppression). - Acute onset, fulminant presentations: less favourable response to corticosteroids (~50%) and should be managed in the context of expectant transplantation (60% needing transplantation; 20% mortality). - Failure to induce remission, or loss of prior response in the young patient must prompt investigation of 'evolving' sclerosing cholangitis.
Maintaining adherence to treatment	- Stratified, personalised approach, best attained through good continuity of care. - Specialist nurses play a vital role in managing chronic disease [50]. Optimised care provision through evaluating, monitoring and education; in addition to facilitating an individualised approach to treatment and follow up that is of greatest efficacy and lowest burden to patients. - Monitoring of thiopurine metabolites facilitates tailoring of therapy and monitoring drug compliance.
Symptomatology and extrahepatic manifestations	- Protective measures for all those on long-term corticosteroids. Consider Budesonide as first line in non-cirrhotic patients with features of metabolic syndrome and/or diabetes mellitus. - Side effects of thiopurines can lead to treatment discontinuation.in 5% to 19% of patients. Improved tolerability can be achieved by starting with lower dosages and titratng according to thiopurine metabolite levels. - Fatigue and arthralgia are recognised symptoms, which may correlate with underlying disease activity. - Pruritus is uncommon compared to that found in chronic cholestatic liver diseases, but may herald an 'evolving' sclerosing cholangitis.
Surveillance of complications	- Bone density measurements at the onset of corticosteroid therapy. - Hepatocellular carcinoma screening for patients with established liver cirrhosis. - Check for gastroesophageal varices according to Baveno guidelines.
Side effects of therapy	- Monitoring of blood glucose and bone density recommended at initiation of systemic corticosteroid therapy. Although precise intervals for surveillance are ill defined, we recommend HbA1c be monitored 6-12 monthly, and bone densitometry 3-5 yearly in the event Prednisolone therapy continues >10 mg/day. Supplementation of vitamin D and adequate calcium intake are commonly advised and added bone-specific therapy according to local practice, taking account of patient-specific (age and sex) and disease-specific (activity and severity) factors. - Monitoring strategy under thiopurine therapy is largely extrapolated

	from data in inflammatory bowel disease (IBD). Checking thiopurine methyltransferase (TPMT) is logical prior to commencement of therapy, and dosing adjusted accordingly, albeit all patients must have monitoring on therapy [54]. - Checking full blood count and renal function is recommended at for example weeks 2, 4, 8 and 12, and then 3-monthly thereafter for patients under therapy with thiopurines, mycophenolate and tacrolimus; principally to screen for cytopenia and cell dyscrasias.

Table 2: Presenting features of adult-onset anti-LKM-1 positive autoimmune hepatitis*

Year of diagnosis	Sex	Diagnosis age (yrs.)	Presentation	Peak serum ALT (IU/L)	Steroid-responsive (Y/N)	Peak serum IgG (g/L) **
2001	Male	21	Acute hepatitis with jaundice	1705	N	13.10
2003	Female	22	Post-partum jaundice	1003	Y	32.77
2004	Female	16	Fatigue	885	Y	15.68
2005	Female	28	Fulminant liver failure	565	Y	14.61
2006	Female	18	Fulminant liver failure	1102	N/A; urgent liver transplant	18.01
2007	Female	24	Post-partum jaundice	780	Y	12.22
2010	Female	19	Acute hepatitis with jaundice	108	N	14.25
2011	Male	33	Abdominal pain	250	Y	10.63
2011	Female	18	Acute hepatitis with jaundice	1031	Y	11.61
2012	Female	27	Acute hepatitis with jaundice	108	Y	14.91
2013	Female	24	Post-partum jaundice	698	Y	14.16
2013	Female	33	Decompensated liver cirrhosis	115	N	15.99

*Incident cases of anti-LKM-1 positive autoimmune hepatitis seen in the Birmingham liver clinic since the year 2000. Only adult onset (diagnosed $\geq$16 yrs. of age) episodes are shown. All patients underwent confirmatory liver biopsy.

** Upper limit of normal for IgG: 16 g/L

Figure 1: Clinical course and patterns of injury in autoimmune hepatitis

[A] Timeline graph of laboratory parameters from the case is shown during the patient's initial presentation and phase of treatment, with black arrowheads indicating the start date of oral Prednisolone at 20mg once daily, and white arrowhead the introduction of Azathioprine. [B] Timeline graph of laboratory parameters from the same patient is shown, who represented after a period of non-attendance to clinic. Black arrowhead indicates re-initiation of Prednisolone and white arrowhead Azathioprine. Single and double asterisks indicate the duration of MMF and Tacrolimus therapy (without Azathioprine), respectively, and black arrow the first infusion of Rituximab. [C] Representative images showing typical features of chronic AIH. From left to right: (i) a portal tract containing a dense lymphoplasmacytic infiltrate associated with moderate interface hepatitis; (ii) interface hepatitis is associated with periportal hepatocyte rosetting and focal emperipolesis; (iii) there is extensive lobular dissection by delicate strands of fibrous tissue, which surround small clusters of hepatocytes forming rosettes (Haematoxylin van-Gieson stain). [D] Representative sections showing changes seen in a case of severe AIH with an acute presentation. From left to right: (i) a plasma cell rich portal inflammatory infiltrate; (ii) lobular hepatitis with prominent plasma cell rich centrilobular inflammation associated with bridging necrosis; and (iii) severe lobular hepatitis with almost pan-acinar necrosis and only occasional small groups of surviving hepatocytes. [E] Evolution of histological changes from a patient having initial diagnosis of AIH that progressed to a PSC predominant phenotype over a three year period, necessitating transplantation due to chronic liver failure and recurrent cholangitis. (i) The first biopsy obtained at diagnosis shows features of acute AIH with prominent lobular inflammation. There is diffuse spotty lobular inflammation associated with hepatocyte ballooning and lobular disarray. The portal tract also contains a moderately dense infiltrate of inflammatory cells. (ii) The second biopsy obtained (750 days) illustrates progression to more typical features of chronic hepatitis with predominant portal inflammation. The portal tract contains a moderately dense infiltrate of mononuclear inflammatory cells. There is focal, mild interface activity but no significant fibrosis is present. Lobular inflammation has resolved. (iii) The hepatectomy specimen obtained at

transplantation (2,982 days) shows a fibro-obliterative duct lesion typical of PSC. A large portal tract contains a nodule of fibrous tissue related to an obliterated bile duct, and peribiliary glands are visible in the bottom right.

AIH, Autoimmune hepatitis; MMF, Mycophenolate Mofetil; PSC, Primary sclerosing cholangitis

Figure 2: Practice tips for managing autoimmune hepatitis

Accurate diagnosis of AIH relies on the collective interpretation of laboratory indices together with liver biopsy review by a dedicated hepatopathologist. Recognising that a characteristic biologic feature of classical AIH is its response to immunosuppression, this reflects something that always needs to be looked for. The diversity in currently proposed treatment algorithms has resulted in wide variations of clinical practice, although corticosteroids remain essential to induce remission. Timely immunosuppression is a proven lifesaving intervention, although a lack of consensus on dosage suggests there is need for more precise markers of disease severity. In any event, a most critical element of effective care delivery centres on securing adherence to therapy, and individualising treatment regimens according to symptoms and tolerability. Uncertainty regarding diagnosis, failure of a patient to attain (or sustain) remission, and acute-severe presentations or incidents of hepatic decompensation are absolute indications for specialist centre referral, given the very real risk of rapid and progressive clinical deterioration and potential need for salvage therapy / transplantation.

AIH, Autoimmune hepatitis

Figure 1

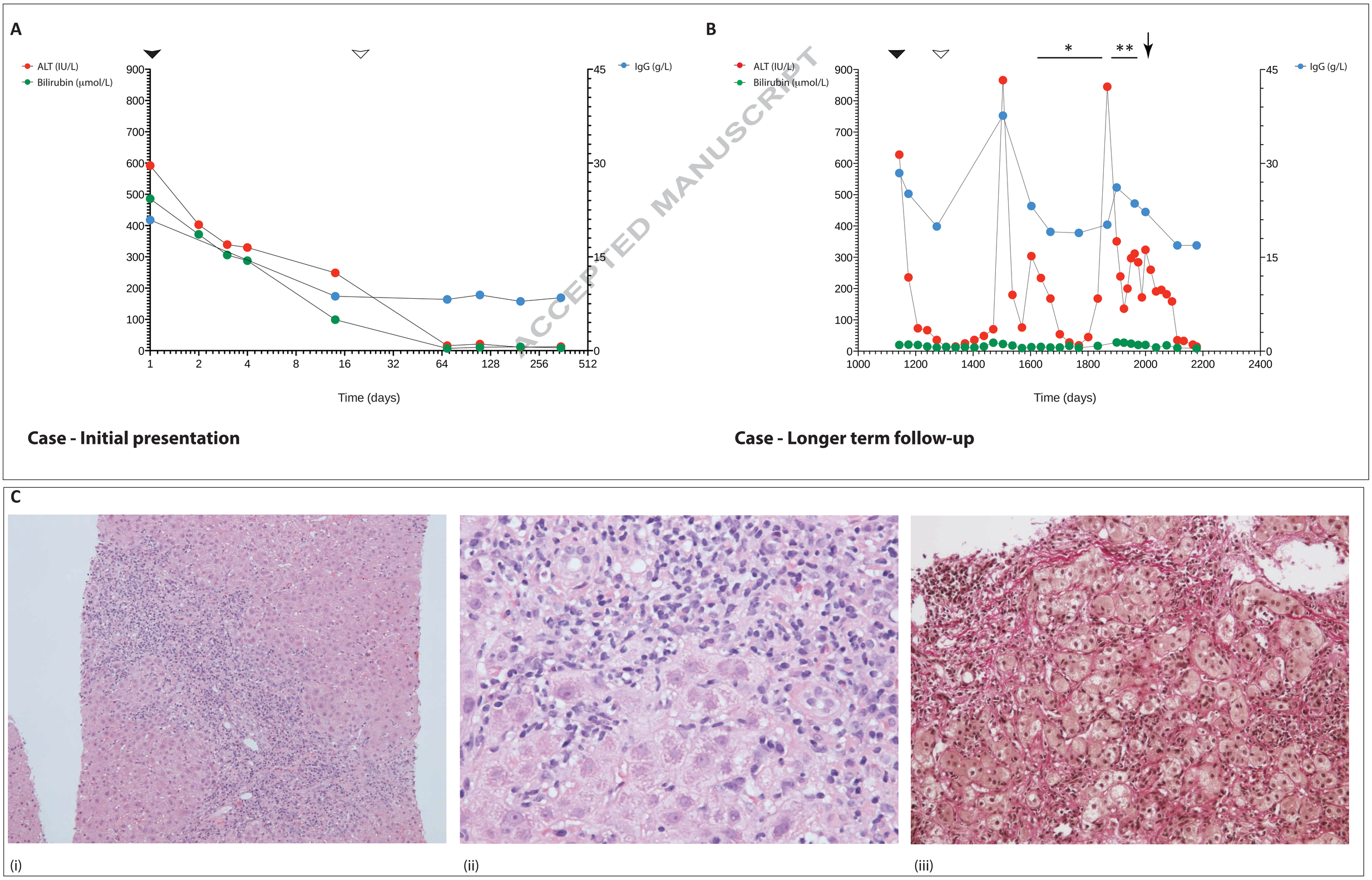

Figure 2